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Effect of passive water absorption on transepithelial movement of extracellular solutes in rat intestine

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Effect of passive water absorption on transepithelial movement of extracellular solutes in rat intestine. It was shown previously that intravenous infusion of saline solution decreases net absorption of sodium and water by rat small intestine and that there is an associated increased movement of inulin from blood into intestinal lumen. It was proposed that decreased absorption may be due to swelling of intercellular channels with widening of the apical cell junction so as to increase inulin movement and extrusion of absorbate back into the intestinal lumen. If this proposal is correct, then a similar increase in permeability to solutes would be expected during passive absorption of hypotonic solution which has been shown to enlarge intercellular channels. In the present study, segments of rat intestine were perfused with isotonic or hypotonic solution. The administration of hypotonic solution increased net water absorption and resulted in a twofold to fourfold increase in the movement of inulin ^{14}C-ferrocyanide or ^{14}C-mannitol from blood into intestinal lumen. The increased permeability for these substances was approximately the same and, therefore, nonselective. Perfusion with a solution with similarly low electrolyte content but made isotonic with mannitol caused no change in permeability. These results are consistent with the view that distension of intercellular spaces occurs during saline infusion or passive absorption of hypotonic solution and this may increase the back flow of absorbate from intercellular channels into intestinal lumen.

Effet de l'absorption passive d'eau sur les mouvements transépithéliaux des substances dissoutes extra-cellulaires dans l'intestin du rat. Il a été antérieurement montré que l'injection intra-veineuse de soluté physiologique diminue l'absorption nette de Na et H_2O par l'intestin grêle du rat, et qu'il se produit une augmentation du mouvement concommittant d'inuline du sang dans la lumière tubulaire. Il a été suggéré que la diminution de l'absorption puisse être due au gonflement des canaux intercellulaires avec élargissement de la jonction cellulaire apicale de telle sorte que le mouvement de l'inuline et le flux en retour d'absorbat vers la lumière intestinale soient augmentés. Si cette hypothèse est valide on doit s'attendre à une augmentation semblable de la permeabilité aux substances dissoutes au cours de l'absorption passive de solution hypotonique dont il a été montré qu'elle détermine un élargissement des canaux intercellulaires. Dans ce travail, des segments d'intestin de rat on été perfusés avec des solutions isotoniques ou hypotoniques. La solution hypotonique a augmenté l'absorption nette d'eau et a eu pour résultat une augmentation d'un facteur 2 à 4 du mouvement de l'inuline, de ^{14}C-FeCN et du ^{14}C-mannitol du sang vers la lumière intestinale. L'augmentation de perméabilité pour ces substances est approximativement la même et, de ce fait, non sélective. La perfusion avec une solution de même concentration faible an électrolytes mais rendue isotonique par l'adjonction de mannitol n'a pas déterminé de modifications de la perméabilité. Ces résultats sont en accord avec l'éventualité de la distension des espaces intercellulaires au cours de l'infusion de soluté physiologique ou de l'absorption passive de solution hypotonique, ce qui peut augmenter le flux en retour de l'absorbat des canaux intercellulaires vers la lumière intestinale.

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Much attention has been given recently to the possibility that intramembraneous extracellular spaces are the anatomical pathways for transepithelial absorption of water and electrolytes, as suggested in the model proposed by Curran and MacIntosh [1]. Intercellular spaces, actual or potential, have been demonstrated to be present in a number of transporting epithelial membranes, including the proximal tubule [2], cortical collecting duct [3], the gall bladder [4] and the intestine [5]. Measurements of electrical conductivity across the proximal tubule of *Necturus* [6] and rat [7] reveal low resistance transepithelial pathways, believed to correspond to lateral intercellular spaces. Molecules which usually do not cross the proximal tubular epithelium have been shown to do so in the rat during hypertonic saline infusion [8] or ureteral or renal venous obstruction [8–10]. It has been proposed that transepithelial movement of these usually impermeant molecules is along intercellular channels rather than across cell membranes.

It has been demonstrated that infusion of isotonic saline solution in the rat or dog [11–13] decreases net sodium and water absorption by the small intestine and infusion of concentrated albumin increases net absorption [11]—changes similar to those occurring in the renal proximal tubule. In studies from this labora-

tory it was observed that decreased intestinal net absorption during volume expansion was accompanied by a several-fold increase in the rate of movement of inulin from blood into intestinal lumen [11]. Infusion of concentrated albumin reversed this leak of inulin in association with increased net absorption of sodium and water. On the basis of these observations it was proposed that the movement of reabsorbate across the epithelial basement membrane and into the capillary circulation is dependent on net oncotic and hydrostatic pressure gradients between basilar and lateral intercellular spaces and the capillary circulation [11]. It was suggested that decreases in capillary absorption (such as would be expected when plasma protein concentration is reduced or capillary hydrostatic pressure is increased) result in an increase in hydrostatic pressure within intercellular channels. This increased pressure could cause distension of spaces between cells and widening of the apical junction of adjacent cells so that some of the intercellular absorbate, together with usually impermeant molecules such as inulin, would leak into the intestinal lumen. Consistent with this proposal are the recent observations of Seely, who found that a reduction in peritubular oncotic pressure caused a fall in electrical resistance across the proximal tubule of rat [7], and those of Keimowitz, in which increased serosal pressure on the isolated gall bladder diminished water transport from mucosa to serosa in association with an increase in inulin permeability from serosa to mucosa [14].

If the aforementioned interpretations are correct, it would be expected that maneuvers other than changes in capillary absorption which might distend intercellular channels would also cause a change in transepithelial permeability. Loeschke, Bentzel and Csaky [5] reported that intercellular spaces in the isolated bullfrog intestine are distended when the lumen is perfused with hypotonic solution so as to promote passive net water absorption. Similar results were observed by Smulders, Tormey and Wright [15] in the isolated rabbit gall bladder. Also, intercellular spaces of the collecting duct *in vitro* [16] and *in vivo* [3] are distended when osmotic absorption of water is accelerated by vasopressin. If, as suggested, the leak of inulin across the rat intestinal epithelium observed during extracellular volume expansion is due to distension of intercellular spaces, then it would be expected also that net absorption of a hypotonic solution would cause an increased permeability to extracellular substances such as inulin. Accordingly, we have examined the effects of passive water absorption by the rat intestine on the transepithelial movement of molecules generally believed to be limited to the extracellular compartment. The results support the view that distension of intercellular spaces, which presumably occurs during passive water absorption, causes a reversible nonselective increase in solute movement from intercellular spaces into the intestinal lumen.

Methods

Studies were performed in 30 male Sprague-Dawley rats weighing 230 to 450 g which were allowed free access to food and water until the time of the experiment. The animals were anesthetized by intraperitoneal injection of Inactin, 100 mg/kg of body weight, and placed on a heated operating table. Surgical procedures and the methods for perfusing jejunal and ileal segments *in situ* were the same as described previously [11]. Measurements of intestinal transport were begun no sooner than 30 minutes after completing the surgical procedures which included cannulation of proximal and distal ends of jejunal and ileal segments and cannulation of a jugular vein and femoral artery for infusion of test substances and collection of samples of blood.

Approximately 10-cm segments of jejunum and ileum were perfused in the proximal-to-distal direction at 191 μl/min, first with an isotonic Tyrode's solution (NaCl, 137; $NaHCO_3$, 11.9; NaH_2PO_4, 0.4; KCl, 3.4; $CaCl_2$, 1.4; $MgCl_2$, 0.1; and glucose, 5 mmoles/liter, respectively; 285 mOsm), then with the same solution diluted threefold with distilled water (hypotonic perfusate, 95 mOsm) in 22 animals or diluted with isotonic mannitol (mannitol/electrolyte perfusate, 291 mOsm) in 8 animals. This procedure was followed by perfusion with the original isotonic electrolyte solution. In four animals both mannitol/electrolyte and hypotonic perfusion were performed with intermediate periods of isotonic electrolyte perfusion. In all studies hypotonic or mannitol perfusion was preceded and followed by perfusion with the isotonic electrolyte solution. Phenolsulfonpthalein (PSP) was added to the perfusion solution and used as the reference marker for volume absorption. Three or more ten-minute consecutive collections for the intestinal effluent were made during each phase of the experiment and at least 20 minutes of perfusion were allowed prior to beginning each set of experimental collections. Net water flux ($J_n^{H_2O}$) was calculated as follows:

$$J_n^{H_2O} = V_i \left(1 - \frac{PSP_i}{PSP_0}\right) \frac{60}{L}$$

where V_i is the perfusion rate in μl/min, PSP_i and PSP_0 are the concentrations of PSP in the perfusate and effluent, respectively, and L is the length of segment perfused (in cm).

Inulin was infused intravenously to maintain a

concentration in plasma of approximately 100 mg/100 ml. In seven of these hypotonic perfusion experiments ^{14}C-mannitol was infused intravenously, in four experiments ^{14}C-ferrocyanide was infused and in three experiments iodinated ^{131}I-serum albumin (RISA-131, Abbott Laboratories, N. Chicago, Ill.) was infused. In the eight experiments with mannitol/electrolyte perfusion, ^{14}C-mannitol was infused intravenously. The infusion of nuclides was calculated to maintain the level of radioactivity in plasma at approximately 10^5 counts per minute (cpm)/ml. The rate of movement of these intravenously infused solutes into the intestinal lumen was expressed as a permeability term (cm^2/hr) calculated as follows:

$$V_0 \left(\frac{E \cdot 60}{P \cdot L}\right)$$

where V_0 is the collected volume of effluent in ml/min and E and P are the concentrations of the specific solute in effluent and plasma, respectively. Values for E were always less than 2% of the value of P and were, therefore, neglected in the denominators of this calculation.

The percentage of recovery of perfused PSP was estimated from the following equation:

$$\frac{V_0 \cdot PSP_0 \cdot 100}{V_i \cdot PSP_i}.$$

In the 22 animals in which net fluxes of water and sodium and unidirectional fluxes (blood to lumen) of inulin, mannitol or ferrocyanide were measured, the recovery of PSP in effluent averaged 91.5 ± 0.8% (SEM) during isotonic perfusion and 90.6 ± 1.4% during hypotonic perfusion. The validity of this calculation requires that a steady state has been achieved between the rate of perfusion and the rate of volume absorption and that volume within the intestinal lumen does not change during the period of collection.[1]

Net sodium flux (J_n^{Na}) was calculated as follows:

$$J_n^{Na} = V_i \left(Na_i - \frac{PSP_i \cdot Na_0}{PSP_0}\right) \cdot \frac{60}{L}$$

where Na_i and Na_0 are the concentrations of sodium in the perfusate and effluent, respectively.

Analytical procedures were the same as described previously [11]. Statistical significance of observed changes was calculated using Student's *t* test and results are expressed as mean ± 1 SEM.

Results

Effect of hypotonic perfusate on net absorption of Na and H_2O and permeability to inulin. Net absorption of Na and H_2O and the simultaneous movement of inulin into the intestinal lumen were measured in both jejunum and ileum in 22 animals before, during and after perfusion with hypotonic Tyrode's solution. The results of these experiments are summarized in Fig. 1. During initial control periods when the intestine was perfused with isotonic solution, the net fluxes of Na and H_2O in jejunum were 16 ± 2 μEq/hr/cm and 109 ± 11 μl/hr/cm, respectively. In ileum these values were 8 ± 2 μEq/hr/cm and 55 ± 10 μl/hr/cm, respectively. This represented absorption of a solution containing 147 and 145 mEq/liter of Na for jejunum and ileum, respectively, and these rates agree well with previously reported values under the same experimental conditions [11]. When the intestinal segments were perfused with the hypotonic solution, net Na flux became negative (net entry into lumen) and averaged −8 ± 1 and −6 ± 2 μEq/hr/cm for jejunum and ileum.

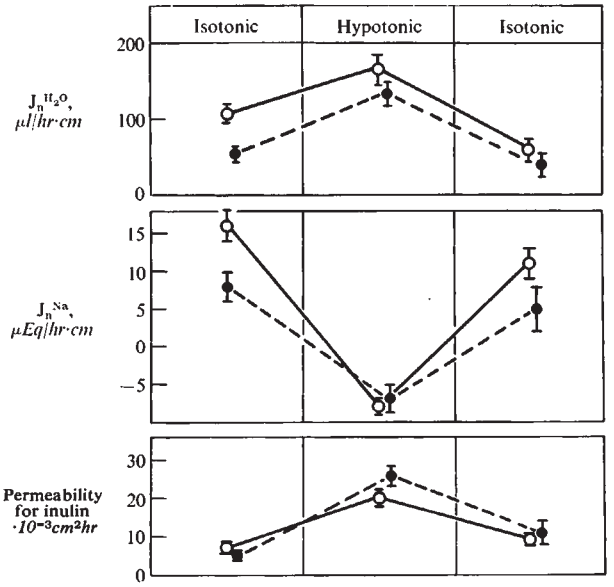

Fig. 1. *Effects of hypotonic perfusate on net transport of water ($J_n^{H_2O}$) and sodium (J_n^{Na}) and inulin permeability in rat intestine.* Values are the means and SEM of at least three consecutive collection periods during each phase of the study in 22 animals. Ileum is represented by the *solid symbols* and jejunum by the *open symbols*. All changes were significantly different from those of preceeding experimental periods ($P < 0.001$).

[1] Although the recovery of PSP measured this way was incomplete, it was unaffected by the hypotonic perfusion. Therefore, the observed qualitative effects of the hypotonic perfusion on $J_n^{H_2O}$ were not due to differences in recovery of PSP. If it is assumed that this incomplete recovery of PSP represents absorption of the marker, then $J_n^{H_2O}$ would be approximately 100 μl/hr/cm greater than the reported values, both during isotonic and hypotonic perfusion. On the other hand, if the incomplete recovery of PSP represents inaccuracies in the rate of perfusion or collection or undetectable leaks of perfusate, $J_n^{H_2O}$ would be approximately 9% greater than the reported values, both during isotonic and hypotonic perfusion. The latter possibility seems more likely [17]. The calculated movements of inulin, mannitol and ferrocyanide from blood to lumen are independent of the degree of recovery of PSP.

Simultaneous net H_2O flux increased to 166 ± 20 and 134 ± 15 μl/hr/cm in jejunum and ileum, indicating absorption of a distinctly hypotonic solution. When isotonic Tyrode's solution was again used as perfusate, values for net Na and H_2O returned close to initial control values in both jejunum and ileum (Fig. 1).

Simultaneously measured permeability to inulin (in the direction of blood to lumen) in these 22 animals during the initial isotonic perfusion averaged $7 \pm 1 \cdot 10^{-3}$ and $5 \pm 1 \cdot 10^{-3}$ cm²/hr for jejunum and ileum, respectively. These values also are similar to those previously reported under these experimental conditions [11]. When the hypotonic solution was used as perfusate, permeability to inulin increased to $20 \pm 2 \cdot 10^{-3}$ and $26 \pm 3 \cdot 10^{-3}$ cm²/hr in jejunum and ileum, respectively (Fig. 1). When the intestinal segments were again perfused with isotonic solution, the movement of inulin decreased towards the initial control values.

Serum albumin-^{131}I was infused intravenously in three of these animals and movement into the intestinal lumen was calculated in the same way as that for inulin. During perfusion with isotonic solution, the permeability for (trichloroacetic acid precipitable) ^{131}I averaged $2 \pm 1 \cdot 10^{-3}$ cm²/hr. This value was unchanged during the hypotonic perfusions and averaged $2 \pm 1 \cdot 10^{-3}$ cm²/hr. These values are the means and SEM for 14 measurements during isotonic perfusion and 15 measurements during hypotonic perfusion.

Permeability to other extracellular markers. In seven of the above experiments ^{14}C-mannitol was infused intravenously together with inulin so that the movement of the two substances into the intestinal lumen could be measured simultaneously. In another four of the above experiments ^{14}C-ferrocyanide was infused intravenously with inulin. During the initial control periods when the intestinal segments were perfused with isotonic solution, the movement of ^{14}C-mannitol and ^{14}C-ferrocyanide into the lumen was low and similar to the simultaneously measured movement of inulin (Table 1). When the perfusate was changed to hypotonic Tyrode's solution, the movement of ^{14}C-mannitol and ^{14}C-ferrocyanide increased in a manner which was quantitatively similar to the simultaneously

Table 1. Simultaneous movement of inulin and another extracellular marker ($\cdot 10^{-3}$ cm²/hr) into intestinal lumen and net water flux before, during and after perfusion with a hypotonic solution

Experiment No.	Isotonic perfusate				Hypotonic perfusate				Isotonic perfusate			
	Inulin	Mannitol	FeCN	$J_n^{H_2O}$ μl/hr/cm	Inulin	Mannitol	FeCN	$J_n^{H_2O}$ μl/hr/cm	Inulin	Mannitol	FeCN	$J_n^{H_2O}$ μl/hr/cm
Jejunum												
12	9		8	126	15		27	233	9		21	90
13	13		4	41	39		15	83	11		12	8
14	7		3	104	26		34	210	11		13	87
15	10		6	172	25		19	186	15		17	44
16	2	6		59	7	18		52				
17	16	9		86	21	11		206	15	13		93
18	11	10			16	24			8	10		
19	23	25		123	23	44		231	2	24		59
20	10	5		76	29	16		158	8	7		31
21	10	15		103	10	20		12	4	6		12
22	4	4		6	36	36		32	19	19		−9
Mean	10.5	11	5	90	22	24	24	140	10	13	16	39
±1 SD	±6	±7	±2	±47	±10	±12	±9	±87	±5	±7	±4	±46
Ileum												
12	2		2	77	2		4	7	1		5	18
13	3		2	76	15		16	226			13	102
14	7		3	35	39		49	212	6		9	35
15	6		1	49	25		12	69	6		8	−29
16	4	5		27	10	15		155				
17	2	5		125	14	6		172	6	6		75
18	14	6			24	30			18	16		
19	3	16		118	25	57		199		9		59
20	1	2		18	13	6		169	3	5		−17
21	17	10		65	46	96		174	17	25		83
22	4	8		97	21	61		178	13	55		223
Mean	6	7	2	69	21	32	20	156	9	19	9	61
±1 SD	±5	±5	±1	±37	±13	±41	±20	±67	±6	±19	±3	±75
P^a					<0.001	<0.05	<0.05	<0.005				

[a] Determined from differences between hypotonic perfusion and the mean value of the isotonic perfusions of jejunum and ileum as paired data.

measured increase in permeability to inulin (Table 1). When the intestinal segments were again perfused with isotonic solution, permeabilities to inulin and simultaneously measured ^{14}C-mannitol or ^{14}C-ferrocyanide returned toward the initial control values. Simultaneously measured net flux of H_2O increased during perfusion with the hypotonic solution and decreased toward the initial control values when the segments were reperfused with isotonic solution (Table 1).

Effect of mannitol/electrolyte perfusate on inulin and mannitol permeability and net Na and H_2O absorption. Mannitol/electrolyte perfusion (isotonic perfusate diluted threefold with isotonic mannitol) was studied in eight rats in order to determine whether dilution of the isotonic electrolyte perfusate without decreasing its osmolality would change the intestinal permeability to inulin or mannitol. The results of these studies are shown in Fig. 2. During initial control periods when the intestine was perfused with isotonic solution, the net fluxes of Na and H_2O in jejunum were 16 ± 4 μEq/hr/cm and 116 ± 25 μl/hr/cm, respectively. In ileum these values were 16 ± 7 μEq/hr/cm and 103 ± 47 μl/hr/cm, respectively, and are similar to those of the previous group of rats. During the mannitol/electrolyte perfusion, there were significant decreases in net Na and H_2O absorption by jejunum which averaged -5 ± 1 μEq/hr/cm and 27 ± 20 μl/hr/cm, respectively. When the jejunum was again perfused with isotonic Tyrode's solution, these values returned close to the initial control values. In contrast, there was no significant change in net Na or H_2O absorption by ileum. Simultaneously measured permeability to inulin and mannitol (blood to lumen) in these same eight animals did not change during perfusion with the mannitol/electrolyte solution in either jejunum or ileum.

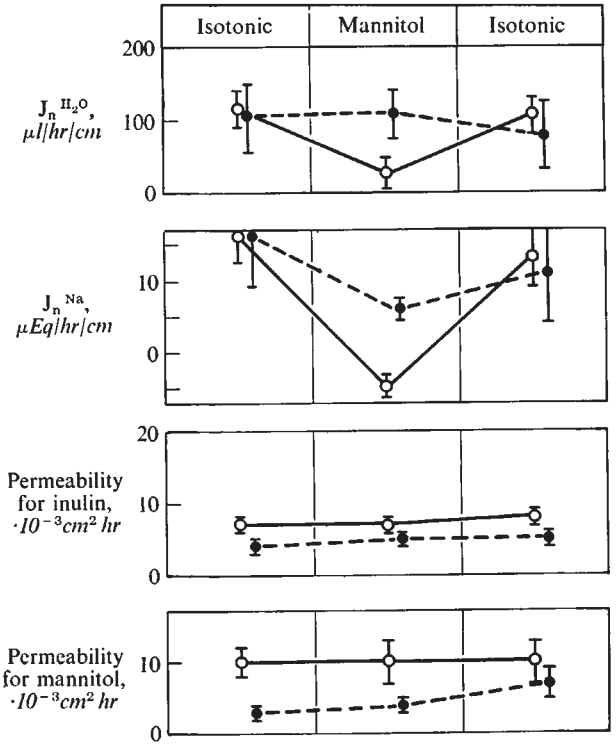

Fig. 2. *Effects of mannitol/electrolyte perfusate on net transport of water ($J_n^{H_2O}$) and sodium (J_n^{Na}) and inulin and mannitol permeability in rat intestine.* Values are the means and SEM of at least three consecutive collection periods during each phase of the study in eight animals.

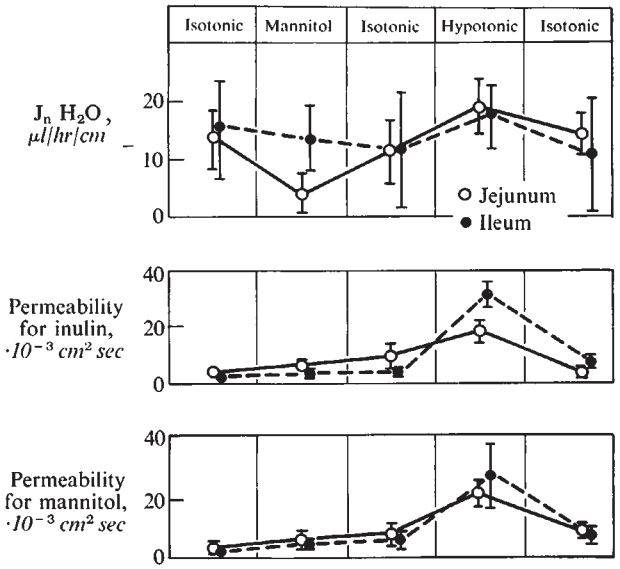

Fig. 3. *Effects of hypotonic electrolyte and mannitol/electrolyte perfusate on net transport of water ($J_n^{H_2O}$) and inulin and mannitol permeability in rat intestine.* Values are the means and SEM of at least three consecutive collection periods during each phase of the study in four animals.

In four animals both mannitol/electrolyte and hypotonic electrolyte perfusates were studied. The results of these experiments are summarized in Fig. 3. While there was no significant change in intestinal permeability during perfusion with the isotonic mannitol/electrolyte solution, when the hypotonic electrolyte perfusate was used there was an increase in permeability to inulin and mannitol which returned to control levels when the isotonic electrolyte perfusate was restored. The changes in net H_2O flux during perfusion with the hypotonic solution were similar to those shown previously in Fig. 1 and 2.

Discussion

When the intestinal lumen was perfused with an isotonic Tyrode's solution, the movement of inulin from blood into lumen was quite low and similar to that previously reported [11]. When a hypotonic

solution was used as the perfusate, net volume absorption by the intestine increased an average of 50% and, at the same time, movement of inulin from blood into intestinal lumen increased threefold. This increased transepithelial movement of inulin was similar to that previously reported for the rat intestine during intravenous saline infusion, even though net volume absorption changed in opposite directions under the two experimental conditions. On the basis of the reasoning outlined above, this observation supports the view that the common change affecting the transepithelial movement of inulin may be distension of channels between adjacent epithelial cells.

When the intestine was perfused with an isotonic solution of low electrolyte content but made isotonic with mannitol, there was no increase in water absorption and no change in permeabilities to mannitol or inulin, indicating that the hypotonicity of the perfusion solution and not dilution of constituent electrolytes resulted in the increased permeability observed during hypotonic perfusions.

In an effort to characterize further this change in permeability of intestinal mucosa, simultaneous measurements were made of the movement of inulin and the smaller extracellular markers, mannitol and ferrocyanide. During perfusion with the hypotonic solution, the transepithelial permeability for all three substances increased and there were no significant differences between the changes in permeability to inulin and that of mannitol or ferrocyanide, suggesting that within the limits of the molecular weights studied (180 to 5,000) the change in permeability was nonselective. This supports the view that distension of intercellular channels may cause widening of apical junctions so as to permit a nonselective flow of intercellular absorbate back into the intestinal lumen. Such a lack of selective permeability would be expected if the epithelial basement membrane is equally permeable to the extracellular markers studied; in a steady state the relative concentration of these markers in the basilar and intercellular spaces will be proportional to their concentrations in plasma. Therefore, the change in transepithelial permeability would be the same for all markers if apical junctions were widened so as to permit unselective flow of solution back into the lumen.

In a previous study it was found that the movement of inulin from blood into lumen increased as intestinal absorption decreased during intravenous saline loading [11]. It is possible that such an increased unidirectional movement of solute could have been the result of diminished resistance to diffusion as volume flux from lumen to blood decreased during saline loading, without necessitating an increased transepithelial permeability to inulin. The present observations make such a conclusion unlikely since, during hypotonic perfusion, solute movements from blood into lumen were increased at a time when volume flux was increased in the opposite direction.

Although the present studies do not provide anatomical evidence of distension of inter-cellular channels, such distension has been shown to occur in the intestine and other epithelia during passive water absorption [3, 5, 15, 16]. These interpretations of the present data lend support for the model in which it was proposed that decreased capillary absorption diminishes net epithelial transport due to distension of intercellular channels, widening of the apical cell junction and extrusion of absorbate back into the intestinal lumen [11]. Although this conclusion provides a rather simple explanation for the changes in solute permeability observed in this and previous studies [11, 15, 18], the possibility cannot be excluded that other effects of the hypotonic perfusion (cellular swelling, altered concentration of intracellular constituents, etc.) affected permeability across cell membranes *per se*. Also, it is possible that net volume flux from lumen to blood and solute (inulin, etc.) flux from blood to lumen occur through separate pathways and the associated changes observed in this and a previous study [11] are only fortuitous.

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